

Supplementary information for the following article:

Cholesterol-lowering treatment in chronic kidney disease: Multistage pairwise and network meta-analyses

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Material S1

Supplementary Methods

According to our intention to produce a two-step summary, the cardiovascular protective efficacy of the strategies based on statins with or without ezetimibe in patients with chronic kidney disease (CKD) was assessed (cholesterol-lowering treatment efficacy evaluation phase); thereafter, low-density lipoprotein cholesterol (LDLc) and C-reactive protein (CRP) were evaluated as potential markers of major adverse cardiovascular events (MACE) in CKD patients who had received such treatment (treatment objectives evaluation phase).

Consequently, a two-stage systematic review design was conceived. With the support of an independent parallel one-stage systematic review, systematic mapping (stage 1) allowed us to perform the cholesterol-lowering treatment efficacy evaluation phase. Subsequently, an in-depth systematic review (stage 2) allowed us to accomplish the treatment objectives evaluation phase.

At the systematic mapping stage, the eligible studies should have compared all strategies using statins alone or combined with ezetimibe and placebo or usual care (the use of a statin was considered usual care if the intervention was a statin at different doses than those planned for the statin used as a comparator or if the intervention was a statin/ezetimibe combination). At the in-depth systematic review stage, the included studies should have compared serum levels of LDLc and/or CRP between patients receiving the intervention and those assigned to the comparator.

MEDLINE via PubMed, Ovid and the Web of Science; EMBASE via Elsevier's Scopus; and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched through September 2018. ClinicalTrials.gov, the EU Clinical Trials Register, and the United Kingdoms' ISRCTN registry were consulted to supplement the internet database searches. Gray literature sources were also scrutinized. DART-Europe E-Theses portal and Open Access Theses and Dissertations were searched to identify relevant PhD and master's theses. Manual searches in meeting abstract archives of the American Society of Nephrology (ASN) Kidney Week 2003 to 2017, the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) congress 2003 to 2018, and the International Society of Nephrology (ISN) World Congress of Nephrology 2001, 2003, 2005, 2007, 2009, 2011, 2013, 2015 and 2017 were performed to identify relevant abstracts. The reference lists of all eligible reports were scanned to identify all relevant studies cited by the included studies. The literature search was restricted to the English language.

Three different review teams, each with specific team conciliators, were formed to select studies (A.M.-B.-M., J.G.-V. and D.M.-G. for the systematic mapping; A.M.-B.-M., F.L.-S. and M.M.C. for the systematic review support of systematic mapping; and D.M.-G., F.H.-G. and M.M.C. for the in-depth systematic review): The screening of titles/abstracts and, subsequently, full-text report examination were carried out by two reviewers independently and disagreements that arose were solved with the participation of a third reviewer who acted as a conciliator. The corresponding authors of the included studies were contacted whenever possible to retrieve missing information and to confirm the study details.

Material S2

Links to registered systematic review protocols and search strategies

Two-stage systematic review

PROSPERO registration ID: CRD42017075166

Systematic review protocol
http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017075166
Search strategy
https://www.crd.york.ac.uk/PROSPEROFILES/75166_STRATEGY_20171221.pdf

One-stage systematic review

PROSPERO registration ID: CRD42017055787

Systematic review protocol
http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017055787
Search strategy
https://www.crd.york.ac.uk/PROSPEROFILES/55787_STRATEGY_20171221.pdf

Table S1. Participants, interventions, comparators, and outcomes in the eligible trials.

Trial	Design	Follow-up (yrs)	Participants/population	Interventions	Comparators	Outcomes	Cointerventions
Detail			Characteristics	(n)	(n)	CVD-related/others	ns
ALERT ^{1,2} International	RCT+EXT	5.1+2	≥65 years/male/DM/CVD (%): [€] 0.0/66.5/17.0/5.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 100.0/0.0 Causes of CKD (%): GN/AID (38.3), TIN/HTN (17.3), Unknown/other (16.1), ADPKD (15.3), DM (13.0).	Fluvastatin 40 mg/d (1050)	Placebo (1052)	MACE ^{&} .	None
4D ^{3,4} Germany	RCT+EXT	4+7.5	≥65 years/male/DM/CVD (%): [£] 68.5/54.0/100.0/47.2 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 100.0/23.7	Atorvastatin 20 mg/d (636)	Placebo (619)	MACE ^{&} . All-cause mortality.	None

			Causes of CKD (%): NA.				
AURORA ⁵ NCT00240331 International	RCT	3.2	≥65 years/male/DM/CVD (%) [£] 77.0/62.1/26.4/39.9 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 100.0/8.0 Causes of CKD (%): TIN/HTN (34.4), ADPKD/other (27.8), DM (19.3), GN/AID (18.5).	Rosuvastatin 10 mg/d (1391)	Placebo (1385)	MACE ^{&} . All-cause mortality, AVF stenosis/thrombosis.	None
Nediat ⁶ Sweden	RCT	3	≥65 years/male/DM/CVD (%) ^{\$} 70.0/69.3/30.8/26.1 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 100.0/0.0 Causes of CKD (%): NA.	Atorvastatin 10 mg/d (70)	Placebo (73)	MACE ^{&}	None
SHARP ⁷	RCT	4.9	≥65 years/male/DM/CVD	Simvastatin	Placebo (4620)	MACE ^{&} .	None

NCT00125593 ISRCTN54137607 UK			(%): ^{\$} 52.5/62.8/22.0/15.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 98.5/0.0 Causes of CKD (%): TIN/HTN (29.0), Unknown/other (28.0), GN (17.0), DM (15.0), ADPKD (11.0).	20 mg/d plus ezetimibe 10 mg/d (4650)			
UK-HARP-II⁸ UK	RCT	0.5	≥65 years/male/DM/CVD (%): ^{\$} 59.5/69.5/11.0/17.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 100.0/0.0 Causes of CKD (%): Unknown/other (41.0), TIN/HTN (26.0), GN/AID	Simvastatin 20 mg/d plus ezetimibe 10 mg/d (102)	Simvastatin 20 mg/d (101)	MACE ^{&} . Safety and tolerability.	None

			(14.0), ADPKD (13.5), DM (5.5).				
ASUCA ⁹ Japan	RCT	2	≥65 years/male/DM/CVD (%): [¥] 66.0/63.8/33.8/7.8 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 100.0/0.0 Causes of CKD (%): NA.	Atorvastatin 20 mg/d (176)	Placebo (173)	MACE ^{&} . eGFR decline.	Dietary and lifestyle counseling. RAAS inhibitor therapy.
ATIC ¹⁰ Netherlands	RCT	2	≥65 years/male/DM/CVD (%): [¥] 44.0/57.0/0.0/0.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 100.0/0.0 Causes of CKD (%): Unknown/other (43.0), HTN (37.0), ADPKD (20.0).	Pravastatin 40 mg/d (47)	Placebo (46)	MACE ^{&} . CC-IMT decrease, BA-FMD increase, eGFR decline, and reduction in UAE, oxLDL and plasma malondialdehyde.	RAAS inhibitor therapy. Vitamins B6, B12 and E.
LORD ¹¹	RCT	3	≥65 years/male/DM/CVD	Atorvastatin	Placebo (68)	MACE ^{&} .	None

Northern Tasmania			(%): [¥] 76.0/65.0/10.0/0.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 100.0/0.0 Causes of CKD (%): ADPKD (44.2), GN (30.6), TIN/HTN (17.1), DM (8.1).	10 mg/d (64)		eGFR decline and reduction in UAE.	
4S ¹² Scandinavian peninsula	PHA of RCT	5.5	≥65 years/male/DM/CVD (%): [¥] 43.0/81.4/4.5/15.4 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 11.4/0.0 Causes of CKD (%): NA.	Simvastatin 20 mg/d (1143)	Placebo (1171)	MACE ^{&} .	None
AFCAPS/ TexCAPS ¹³ USA	PHA of RCT	5	≥65 years/male/DM/CVD (%): [¥] 22.0/87.9/2.3/0.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 4.6/0.0	Lovastatin 40 mg/d (3301)	Placebo (3304)	MACE ^{&} .	None

			Causes of CKD (%): NA.				
ALLHAT ¹⁴ NCT00000542 USA	PHA of RCT	4.8	≥65 years/male/DM/CVD (%): [‡] 87.0/51.5/35.1/36.5 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 15.4/0.0 Causes of CKD (%): NA.	Pravastatin 40 mg/d (5085)	Usual care (5066)	MACE ^{&} .	Nonstatin lipid-lowering medications (physician's judgement).
ALLIANCE ¹⁵ USA	PHA of RCT	6	≥65 years/male/DM/CVD (%): [‡] 80.0/82.2/22.1/64.5 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 23.7/0.0 Causes of CKD (%): NA.	Atorvastatin 10 mg/d (1217)	Usual care (1225)	MACE ^{&} . All-cause mortality.	Nonstatin lipid-lowering medications (physician's judgement).
CARDS ¹⁶ NCT00327418 UK	PHA of RCT	4	≥65 years/male/DM/CVD (%): [‡] 50.0/68.0/100.0/0.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 34.2/6.5	Atorvastatin 10 mg/d (1428)	Placebo (1410)	MACE ^{&} .	None

			Causes of CKD (%): NA.				
IDEAL ¹⁷ Norway	PHA of RCT	4.8	≥65 years/male/DM/CVD (%): [‡] 80.8/60.0/12.0/51.3 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 26.2/5.0 Causes of CKD (%): NA.	Atorvastatin 80 mg/d (4439)	Simvastatin 20 mg/d (4449)	MACE ^{&} . eGFR decline.	None
JUPITER ¹⁸ NCT00239681 International	PHA of RCT	5	≥65 years/male/DM/CVD (%): [‡] 82.3/61.8/0.0/0.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 18.0/5.0 Causes of CKD (%): NA.	Rosuvastatin 20 mg/d (8901)	Placebo (8901)	MACE ^{&} .	None
LIPS ¹⁹ International	PHA of RCT	3.9	≥65 years/male/DM/CVD (%): [‡] 94.0/84.1/12.2/100.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 19.9/4.0	Fluvastatin 40 mg/d (781)	Placebo (777)	MACE ^{&} . Safety and tolerability.	Dietary and lifestyle counseling.

			Causes of CKD (%): NA.				
MEGA ²⁰ NCT00211705 Japan	PHA of RCT	5.3	≥65 years/male/DM/CVD (%):¥ 60.0/23.1/19.8/0.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 41.3/0.0 Causes of CKD (%): Unknown/other (59.0), HTN (30.0), DM (11.0).	Pravastatin 20 mg/d (3533)	Placebo (3663)	MACE&. eGFR decline.	Dietary and lifestyle counseling.
SAGE ²¹ USA	PHA of RCT	1	≥65 years/male/DM/CVD (%):¥ 100.0/69.3/23.3/100.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 48.7/0.0 Causes of CKD (%): NA.	Atorvastatin 80 mg/d (433)	Pravastatin 40 mg/d (425)	MACE&. eGFR decline and safety and tolerability.	None
TNT ²²	PHA of	4.9	≥65 years/male/DM/CVD	Atorvastatin	Atorvastatin	MACE&.	None

NCT00327691 USA	RCT		(%): [¥] 38.2/81.1/14.8/100.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 32.2/10.0 Causes of CKD (%): NA.	80 mg/d (4827)	10 mg/d (4829)	eGFR decline.	
WOSCOPS-CARE- LIPID ²³ International	PHA of RCTs		≥65 years/male/DM/CVD (%): [¥] 42.5/89.1/7.2/54.8 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 26.7/0.0 Causes of CKD (%): NA.	Pravastatin 40 mg/d (9338)	Placebo (9217)	MACE ^{&} . eGFR decline.	None
PREVEND IT ^{24,25} Netherlands	RCT+EXT 2x2 factorial design	4+5.5	≥65 years/male/DM/CVD (%): [¥] 33.0/64.9/2.5/1.0 KDIGO GFR G3a–G5/LDLc <100 md/dl (%): 0.0/0.0 Causes of CKD (%): NA.	Pravastatin 40 mg/d (433)	Placebo (431)	MACE ^{&} .	Fosinopril 20 mg/d

[€]All participants were patients who had undergone kidney transplantation [ALERT (the Assessment of LEscol in Renal Transplantation) Study]. [£]All participants were chronic dialysis patients (HD and PD) [studies: 4D (Die Deutsche Diabetes Dialyse), AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events)]. [§]Participants were individuals with NKF/CKD KDIGO GFR categories G1–G2, patients with CKD KDIGO GFR categories G3a–G5, and patients treated with chronic dialysis [studies: NediAt, SHARP (Study of Heart And Renal Protection), UK-HARP-II (the second United Kingdom Heart and Renal Protection study)]. [¥]Participants were individuals with NKF/CKD KDIGO GFR categories G1–G2 and patients with CKD KDIGO GFR categories G3a–G5 but not dialysis patients [studies: ASUCA (ASsessment of clinical Usefulness in CKD patients with Atorvastatin), ATIC (the Antioxidant Therapy In Chronic renal insufficiency), LORD (the Lipid lowering and Onset of Renal Disease), 4S (the Scandinavian Simvastatin Survival Study), AFCAPS/TexCAPS (the Air Force/Texas Coronary Atherosclerosis Prevention Study), ALLHAT (the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), ALLIANCE (the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events), CARDS (the Collaborative AtoRvastatin in Diabetes Study), IDEAL (the Initiating Dialysis Early And Late), JUPITER (Justification for the Use of statins in Primary prevention—an Intervention Trial Evaluating Rosuvastatin), LIPS (Lescol Intervention Prevention Study), MEGA (Management of Elevated cholesterol in the primary prevention Group of Adult Japanese), SAGE (the Study Assessing Goals in the Elderly), TNT (Treating to New Targets), WOSCOPS (West of Scotland Coronary Prevention Study)-CARE (Cholesterol And Recurrent Events)-LIPID (Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), PREVEND IT (the Prevention of REnal and Vascular ENdstage Disease Intervention Trial)]. [&]MACEs included all fatal and non-fatal coronary events including revascularization procedures and all cerebrovascular events including TIA. Abbreviations: ADPKD, autosomal-dominant polycystic kidney disease; AID, autoimmune disease; AVF, arteriovenous fistula; BA-FMD, brachial artery flow-mediated dilatation; CC-IMT, common carotid intima-media thickness; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; EXT, follow-up extension; GN,

glomerulonephritis; HD, hemodialysis; HTN, hypertension; KDIGO; Kidney Disease: Improving Global Outcomes; KTR, kidney transplant recipient; LDL-c; low-density lipoprotein cholesterol; MACE, major adverse cardiac event; NA, not available; NKF, normal kidney function; ox-LDL, plasma-oxidized low-density lipoprotein; PD, peritoneal dialysis; PHA, post hoc analysis; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; TIA, transient ischemic attack; TIN, tubulo-interstitial nephritis; UAE, urinary albumin excretion.

Table S2. Assessing risk of bias in the eligible trials.

Trials	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
ALERT	L	L	L	U	U	L	U
4D	L	L	L	L	U	L	U
AURORA	L	L	L	L	L	L	U
Nediat	L	L	U	U	U	L	U
SHARP	L	L	L	L	L	L	U
UK-HARP-II	L	L	U	U	U	L	U
ASUCA	L	L	U	U	U	L	U
ATIC	L	L	L	U	U	L	U
LORD	L	L	L	L	U	L	U
4S	L	L	U	U	U	U	U
AFCAPS/TexCAPS	L	L	U	U	U	U	U

ALLHAT	L	L	U	U	L	U	U
ALLIANCE	L	L	U	U	U	L	U
CARDS	L	L	U	U	L	U	U
IDEAL	L	L	U	U	U	U	U
JUPITER	L	L	U	U	L	U	U
LIPS	L	L	U	U	U	U	U
MEGA	L	L	U	U	L	U	U
SAGE	L	L	U	U	U	U	U
TNT	L	L	U	U	L	U	U
WOSCOPS-CARE- LIPID	L	L	U	U	U	U	U
PREVEND IT	L	L	L	U	U	L	U

The judgement for each of risk of bias domain is presented as (L), (U) or (H) to indicate low, unclear, or high risk of bias, respectively.

Table S3. Evaluation of codependent health technologies .

Information requests	Comments
Section 1 – Context	
Details about the biomarker, the test and the medicine	
1 (O) Current reimbursement arrangements.	The medicines and the test are available in developed countries, and the costs are affordable in most developing countries.
2 (T) Test sponsor.	Many sponsors are available.
3 (M) Medicine sponsor.	Many sponsors are available.
4 (O) Biomarker.	Serum levels of LDLc and CRP.
5 (T) Proposed test.	Determination of serum levels of LDLc and CRP.
6 (O) Medical condition or problem being managed.	CVD risk in patients with CKD.
7 (O) Clinical management pathways.	Treatment evaluation.
Rationale for the codependency	
8 (O) Definition of the biomarker.	Reduction in the levels of LDLc and CRP.
9 (O) Biological rationale for targeting that biomarker(s).	The risk of MACEs is lower when LDLc and CRP are reduced by treatment with the medicines.
10 (O) Other biomarker(s) to assess treatment effect of the medicine.	None.
11(O) Prevalence of the condition being	15%

targeted in the population that is likely to receive the test.	
Proposed impact of codependent technologies on current clinical practice	
12 (T) Consistency of the test results over time.	In the follow-up periods of the eligible studies, a low frequency of MACEs was observed when LDLc and CRP were reduced via treatment with the medicines.
13 (T) Use of the proposed test with other treatments and/or for other purposes.	NA
14 (T) Use of the test in the clinical management pathway.	The test is most likely to be an additional test to manage patients.
15 (T) Provision of the test.	The test is routinely used in hospitals of developed countries.
16 (T) Specimen or sample collection.	Peripheral blood.
17 (T) Use of the test for monitoring purposes (if relevant)	Treatment evaluation but not aiming for the titration of medicines.
18(O) Availability of other tests for the biomarker.	None.
Section 2 – Clinical evaluation	
Direct evidence approach	
Section 2a Evidence of prognostic effect of the biomarker	
19(O) Prognostic effect of the biomarker.	It can be assumed methodologically.
Section 2d Clinical evaluation of the codependent technologies (combined)	

20(O) Selection of the direct evidence.	Low-level direct evidence is available (retrospective biomarker-stratified trials).
21(O) Quality of the direct evidence.	The evidence is of adequate quality.

Item numbers are tagged with (T), (M) or (O), which indicate whether the item number is relevant to the test, the medicine or overlaps with both. Abbreviations: CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; LDLc, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

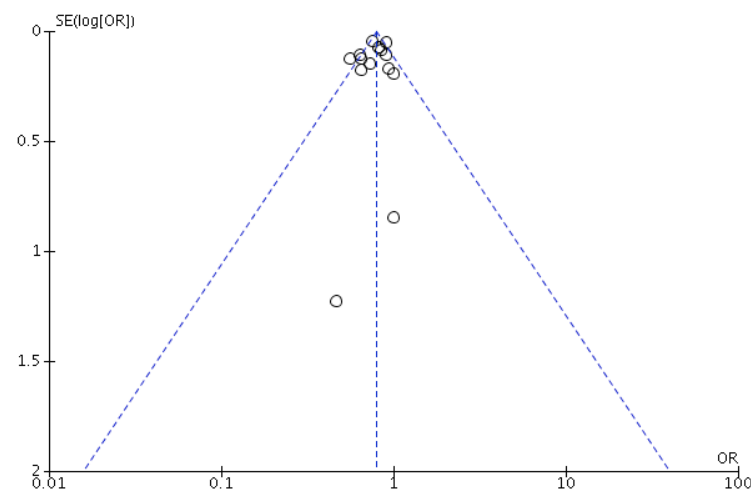
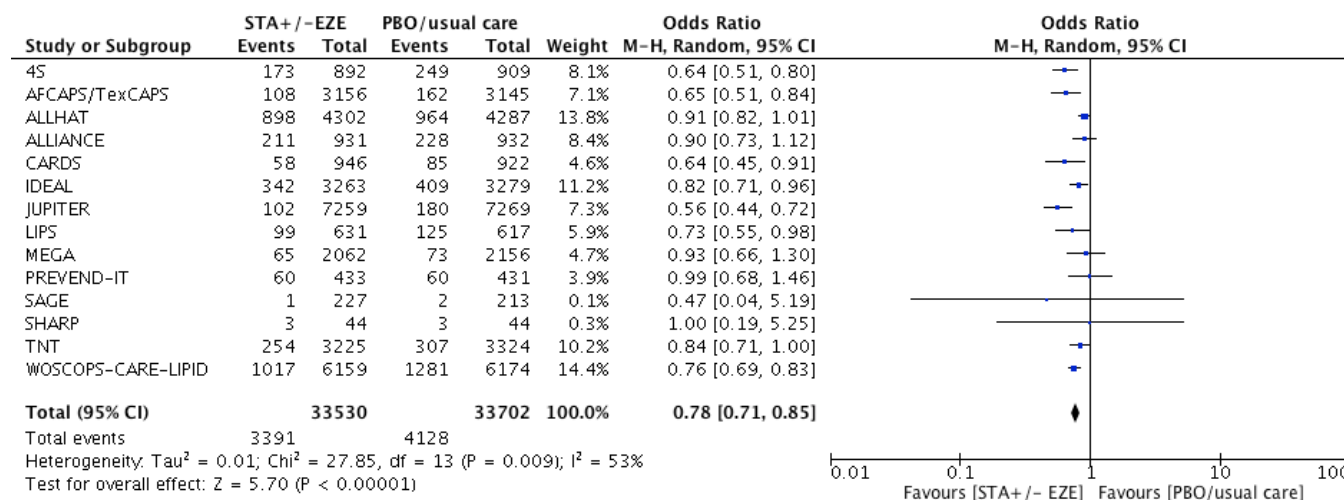


Figure S1. The effect of cholesterol-lowering treatment on MACEs when the eGFR is 60 ml/min/1.73 m² or higher. CI, confidence interval; eGFR, estimated glomerular filtration rate; EZE, ezetimibe; M-H, Mantel–Haenszel test; PBO, placebo; SE, standard error; STA, statins.

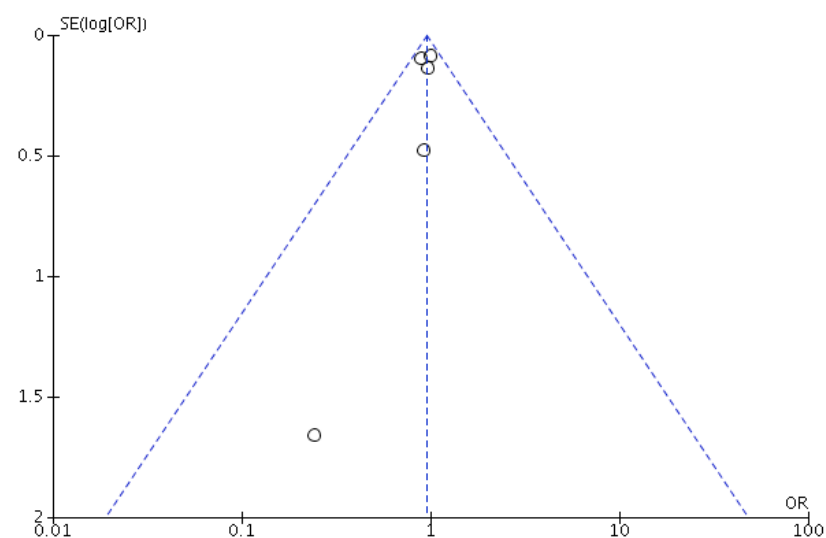
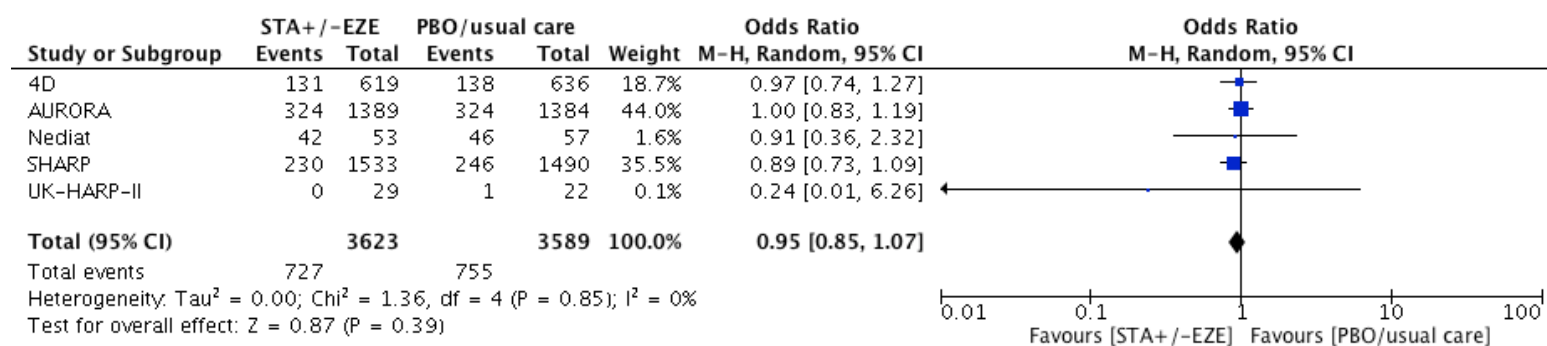


Figure S2. The effect of cholesterol-lowering treatment on MACEs in dialysis patients. CI, confidence interval; EZE, ezetimibe; M-H, Mantel–Haenszel test; PBO, placebo; SE, standard error; STA, statins.

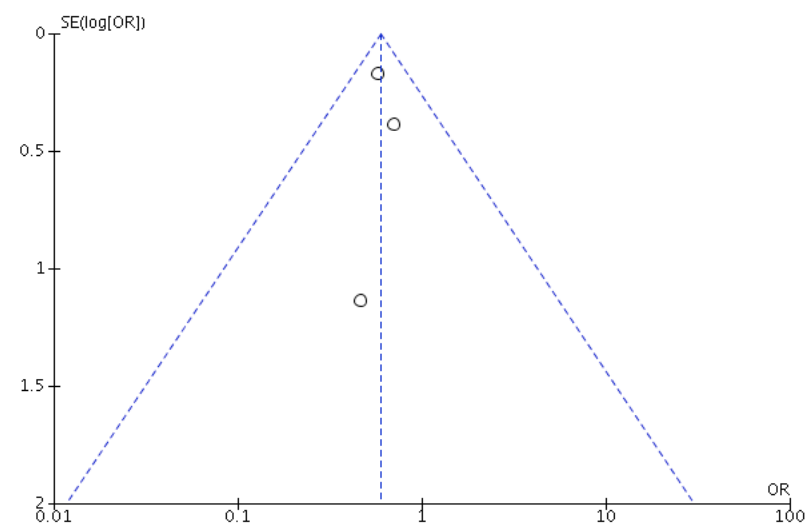
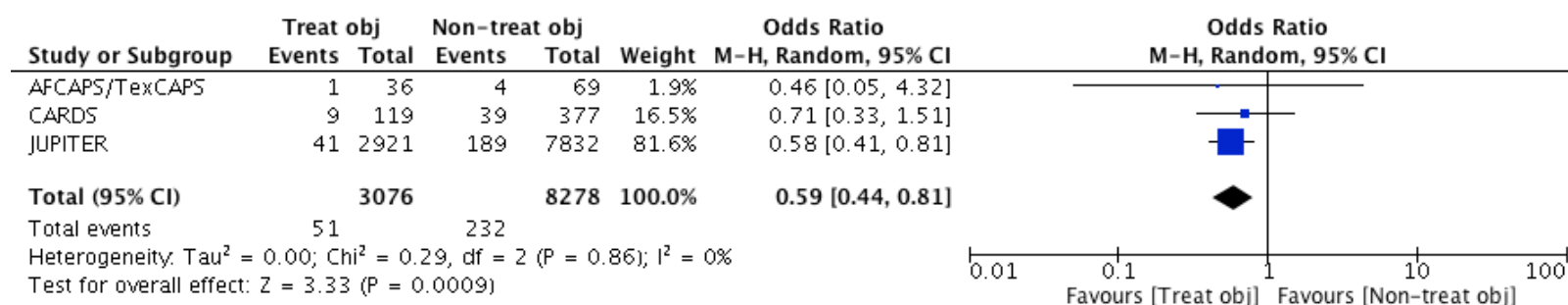


Figure S3. The effect of a combined reduction in LDLc and CRP of less than 50% regardless of eGFR. CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDLc, low-density lipoprotein cholesterol; M-H, Mantel–Haenszel test; SE, standard error.

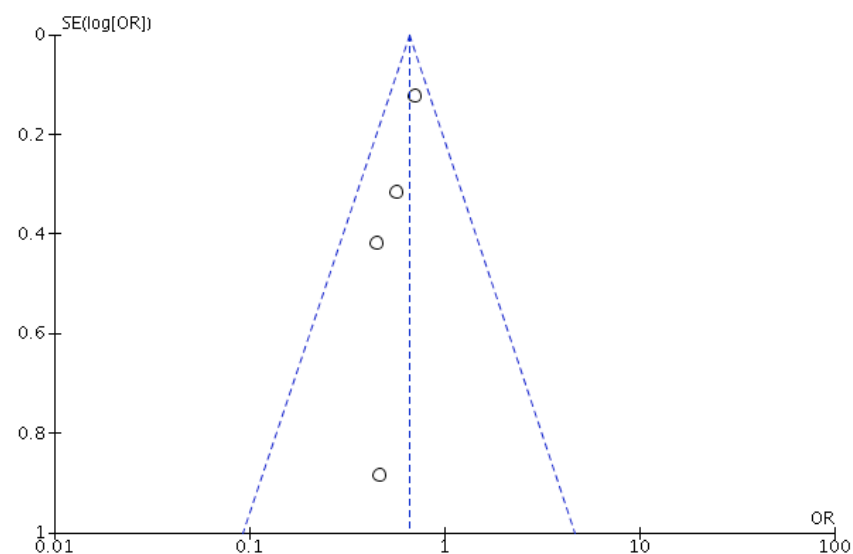
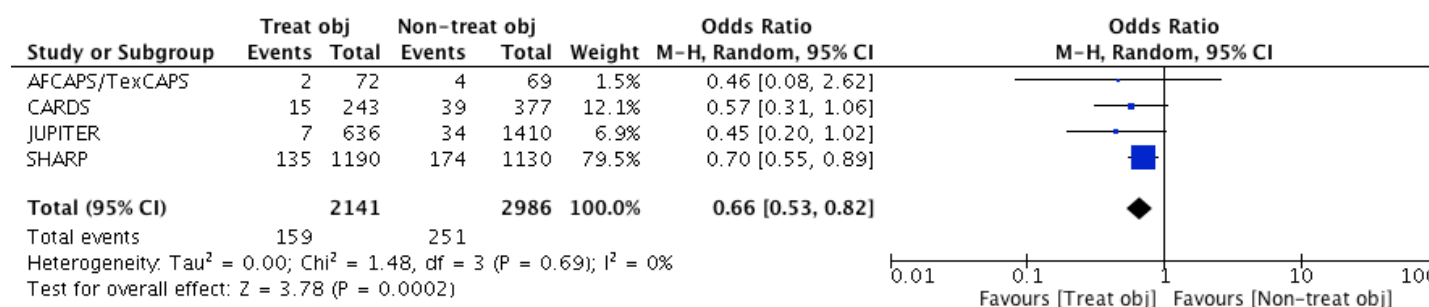


Figure S4. The effect of a reduction in LDLc of less than 50% regardless of eGFR. CI, confidence interval; eGFR, estimated glomerular filtration rate; LDLc, low-density lipoprotein cholesterol; M-H, Mantel–Haenszel test; SE, standard error.

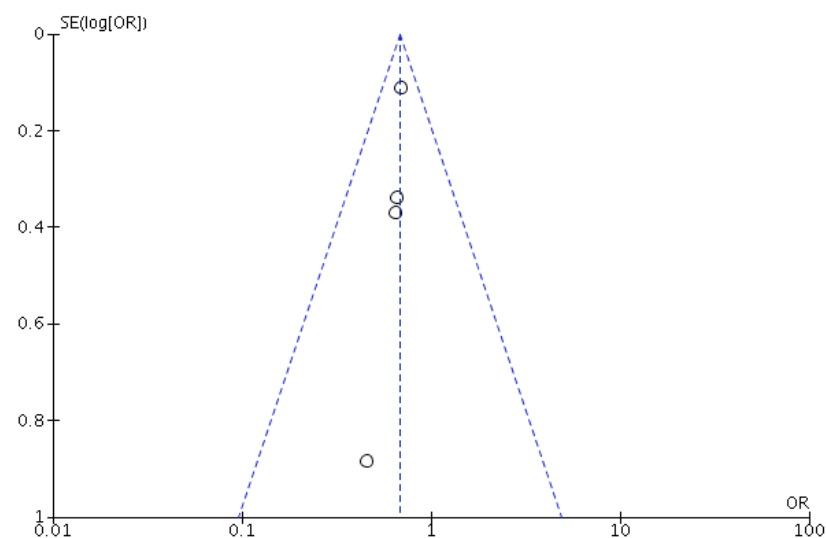
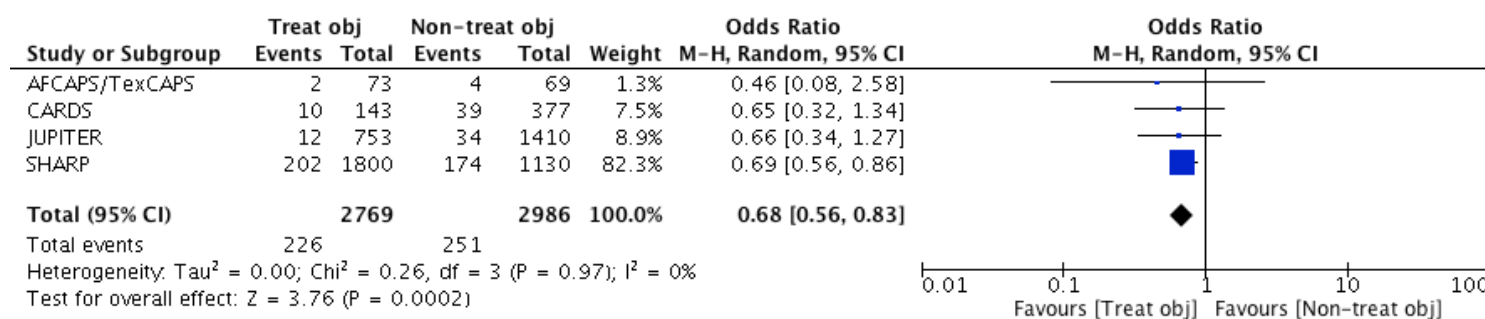


Figure S5. The effect of a reduction in LDLc of 50% or higher regardless of eGFR. CI, confidence interval; eGFR, estimated glomerular filtration rate; LDLc, low-density lipoprotein cholesterol; M-H, Mantel–Haenszel test; SE, standard error.

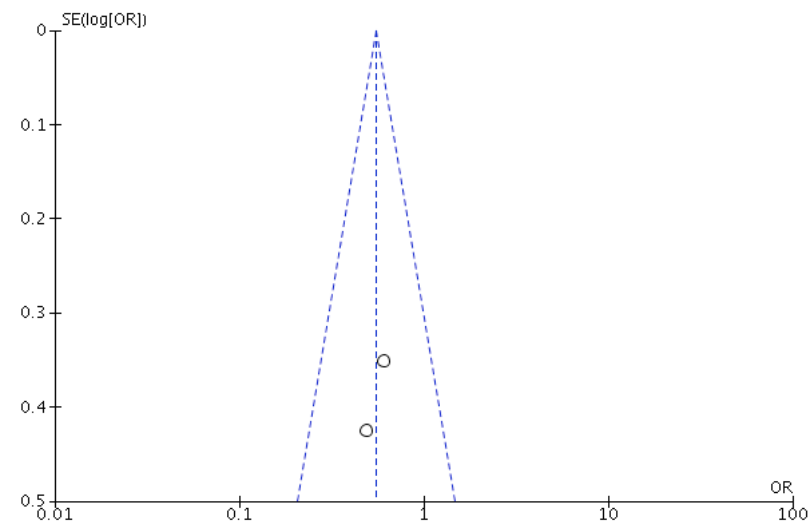
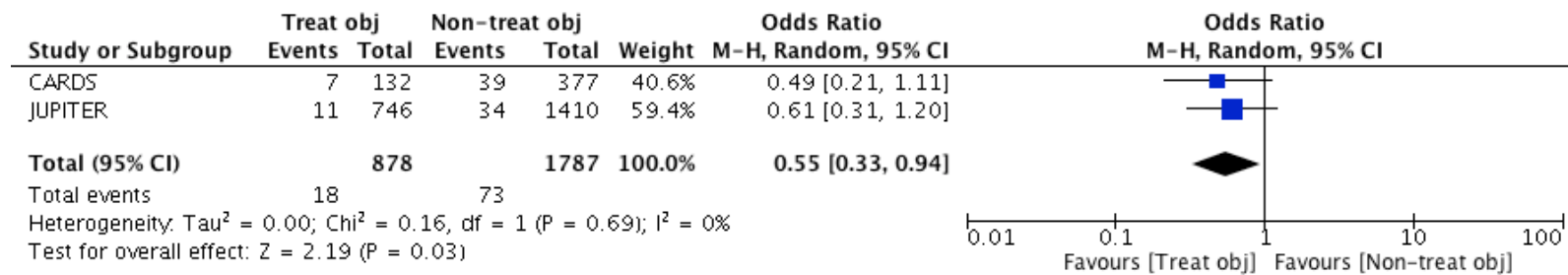


Figure S6. The effect of a reduction in CRP of less than 50% regardless of eGFR. CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; M-H, Mantel–Haenszel test; SE, standard error

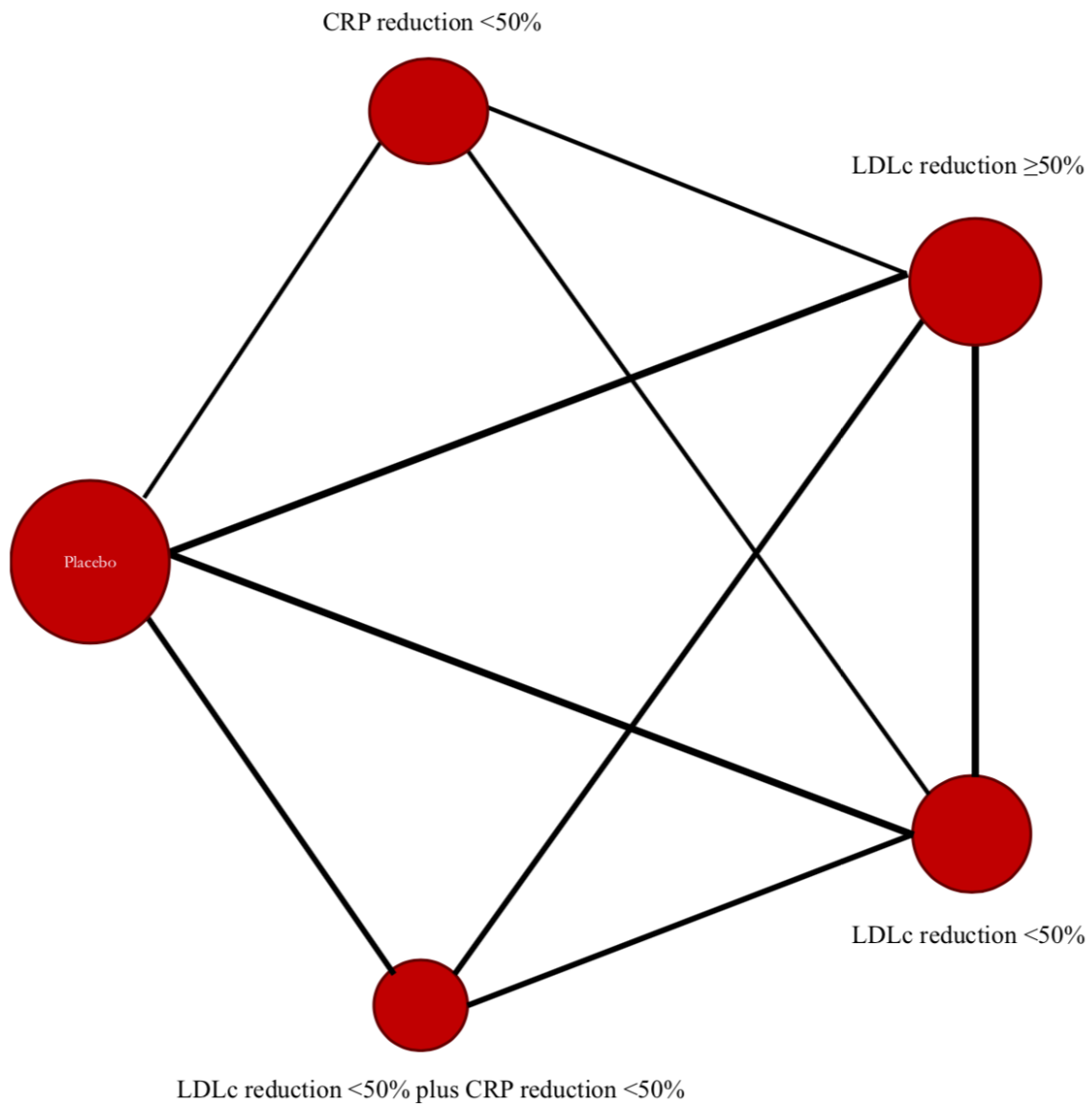


Figure S7. Network diagram of the LDLc and CRP treatment objectives regardless of eGFR and not including dialysis patients (Markov chain Monte Carlo simulation). CRP, C-reactive protein; LDLc, low-density lipoprotein cholesterol.

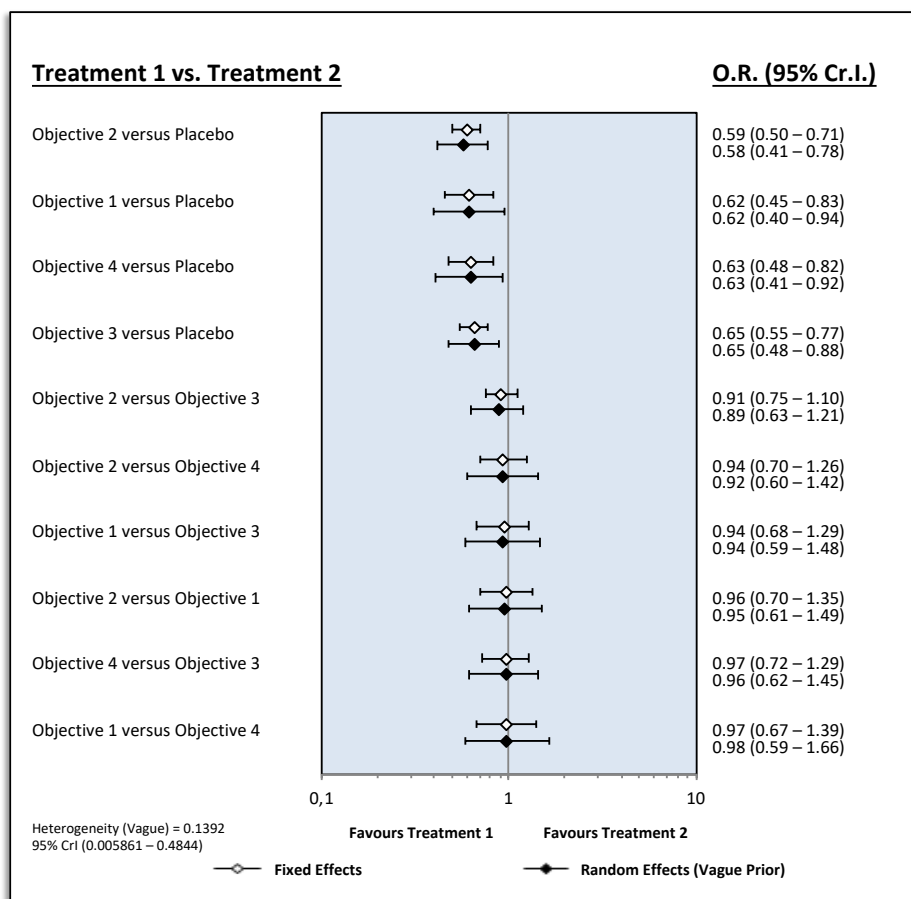


Figure S8. Network forest plot of fixed and random effects for the LDLc and CRP treatment objectives.

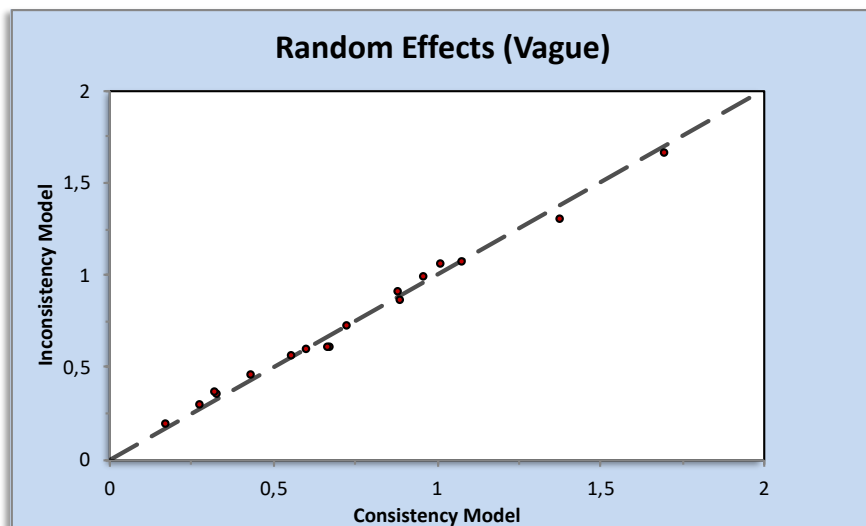


Figure S9. Inconsistency plot of the random effects for the LDLc and CRP treatment objectives.

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